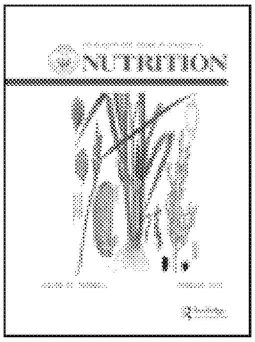

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Original Paper

Mineral Composition of Meconium: Effect of Prematurity

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Key words: meconium, minerals, prematurity, birth weight

Objectives: We hypothesized that the concentration of major essential mineral elements in meconium correlate with gestational age (GA) or birth weight. To verify this premise we determined the concentration in meconium of calcium, magnesium, phosphorus, copper, zinc, iron, and manganese.

Methods: Thirty-four appropriate for age singleton infants without major congenital anomalies were divided into four GA groups (in weeks): 24 to 28; 29 to 33; 34 to 37; 38 to 42, or in birth weight groups (in g): <1500; 1500–1999; 2000–2499; ≥2500. Meconium was collected until the appearance of transitional stools and lyophilized for analysis.

Results: When adjusted for birth weight, the concentrations of calcium, copper, iron and phosphorus were higher in the meconium of 24 to 28 week GA infants than in those of the 38 to 42 week GA newborns. Birth weight adjusted copper concentration was highest in the 29 to 33 week GA group, while the remaining elements did not change across the range of GA. Meconium copper concentration in infants born with <2000 g was higher than in those born with a weight ≥2500 g.

Conclusions: These results could serve as normative data of a noninvasive examination of the mineral nutritional "history" of the fetus, and, eventually, to better evaluate possible neonatal deficiencies in infants with intrauterine growth retardation or other types of complicated intrauterine courses.

INTRODUCTION

It is well accepted that the nutritional status of the pregnant woman affects the outcome of her pregnancy. Since most nutrients, including minerals and trace elements, are transported and stored in the fetus in relatively large amounts during the last trimester, potential nutritional deficits may be critical in the premature infant. Their replacement, during the first few weeks of life, is a significant challenge for the neonatologist.

Meconium, which is the dark viscous stool passed by the newborn in the first few days of life, may provide an index of mineral accumulation by the fetus, since the fetus does not normally excrete stools in utero. To date, there has been only scant information on the appearance of nutritionally significant mineral elements in meconium, both in term and premature infants, but without establishing any relationship with gestational age (GA) and/or birth weight [1–4].

We hypothesize that the concentration in meconium of major mineral elements of nutritional significance may correlate with GA or birth weight. Furthermore, the concentration of these elements, when adjusted by birth weight, could further clarify whether the concentration of each element in meconium remains constant, regardless of GA, or that deposition in meconium occurs at a uniform rate and tends to decrease in absolute concentration as other meconium constituents are excreted.

The specific aim of this study was to determine the concentration and total amount of certain mineral elements: calcium, magnesium, phosphorus, copper, zinc, iron and manganese in the meconium of preterm and full term infants and to evaluate the concentration changes of these minerals with GA or birth weight.

MATERIALS AND METHODS

Meconium was collected from the infants admitted to the neonatal intensive care unit and regular nursery at North Shore University Hospital. Only singleton infants irrespective of sex and race, who were appropriate for GA and without major cardiac, central nervous system or gastrointestinal malformations were included. At the time of meconium collection the

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newborn were receiving intravenous fluid and electrolyte support, but no total parenteral nutrition. All mothers had adequate prenatal care and received routine nutritional advice. GA was evaluated according to maternal last menstrual period, with confirmation by fetal ultrasound. The meconium was collected until appearance of transitional stools, which were defined as a change in the color and/or consistency of fetal excreta from dark and viscous to yellowish green and non-viscous. The meconium was removed from the diapers with a wooden scoop and kept frozen until the collection from each infant was completed. The entire meconium sample was lyophilized (Virtis Co., Gardiner, NY) from polystyrene containers and the dehydrated mass weighed and thoroughly mixed prior to the assay of aliquots. Samples weighing approximately 0.10–0.15 g were transferred to test tubes and treated with 2.0 mL of trace element grade concentrated nitric acid (Fisher Chem. Co., Pittsburgh, PA), with occasional shaking, until digestion was completed. The digesta were diluted to 10 mL, centrifuged at 500×g and filtered to remove insoluble material. The samples were analyzed for calcium, magnesium, copper, zinc, iron and manganese by atomic absorption spectrophotometry (SpectrAA10, Varian Instruments, Inc., Sunnyvale, CA) against external standards. Phosphorus was assayed by a spectrophotometric method [5]. The results were corrected for appropriate reagent and matrix blanks. For evaluation of data, the patients were grouped either by GA, or by birth weight, as follows:

By GA (in weeks): 24 to 28; 29 to 33; 34 to 37; 38 to 42.

By birth weight (in g): <1500; 1500–1999; 2000–2499; ≥2500.

As shown in tables and figures, results were expressed as μg of each element per g of dry meconium to avoid errors from possible incomplete collection [3,4] and as μg/g (= ppm)/kg body weight at birth, as a function of the GA. This correction allows testing the premise that mineral concentration increases with birthweight. Results for each GA and birth weight group were compared by the Kruskal-Wallis test with nonparametric multiple contrasts [6]. Trends were assessed by Cuzick's test [7]. The study was designed under the assumption that we would find differences between 100 and 200% among the groups, each of them having a coefficient of variation of 100%. Under these conditions, we would require between four and 16 infants per group for a power analysis of 80%. The data presented here correspond to a total of 34 individual specimens with the demographic characteristics presented in Table 1. This study was approved by the Institutional Review Board.

Table 1. Gestational Age (GA), Weight Range and Sex Distribution of the Study Population

GA (weeks)	Weight range (g) (median)	M/F
38–42	2510–3915 (3350)	7/2
34–37	1605–2590 (2052)	4/8
29–33	1138–2140 (1752)	4/4
24–28	550–1233 (1111)	3/2

RESULTS

The data presented here show that considerable changes occur in the mineral content of meconium, either when related to the GA or the birth weight of the infant. Our results regarding the concentration of the various minerals as a function of GA revealed that zinc was significantly lower in the meconium of the 24 to 28 week old newborns than in the meconium of full term (38 to 42 week) infants (Table 2). Meconium copper attained maximal concentration in the 29 to 33 week GA group. These values, as well as those of the 34 to 37 week newborns were higher than those of full term infants. Iron reached peak values in the meconium of infants 34 to 37 week GA. Calcium concentration was highest in the 24 to 28 week premature infants. In contrast, the meconium concentration of magnesium, phosphorus and manganese exhibited no differences regardless of the GA of the newborn. Calcium and magnesium were excreted in the meconium of the smallest premature infants at the highest concentration, when compared to any other element. While calcium was the most abundant of the minerals examined in meconium at 24 to 28 weeks, magnesium was in the highest content in the meconium of newborn infants with a GA of ≥29 weeks.

In terms of the absolute concentration of minerals, beyond 29 week GA, the values for magnesium were the highest of all elements included in the study (Table 2). Meconium calcium was highest in the earliest born infants, as compared to newborns of other GA. Conversely, zinc concentration was the lowest in the meconium of the 24 to 28 week GA group. Copper and iron meconium content peaked at 29 to 33 week GA and 34–37 week GA, respectively. Manganese was present in all meconium specimens at one order of magnitude or less than other trace elements.

When meconium mineral concentration was assessed by birth weight groups (Table 3), only copper content exhibited differences: the infants born with <1500 g and between 1500 and 1999 g had higher meconium copper than the heaviest newborns. When mineral concentration in the meconium at various GA was adjusted for birth weight, the values for calcium were highest in the 24 to 28 week group, and were greater in the 29 to 33 and 34 to 37 week groups than in the full term infants (Fig. 1). Magnesium was present at a higher concentration in the specimens of the 24 to 28 and 29 to 33 week newborns than in those of the 38 to 42 week infants. The progressive decrease trend of birth weight adjusted concentration as GA increased was very significant, both for calcium ($p=0.0003$) and magnesium ($p=0.0036$) [7]. Likewise, the birth weight adjusted meconium copper, iron and phosphorus were lowest in the full term infants, as compared to those of 24 to 28, 29 to 33 and 34 to 37 week GA (Fig. 2). The declining trend as a function of greater GA was significant for phosphorus ($p=0.0002$), copper ($p<0.0001$) and iron ($p=0.0006$). Only the values of meconium zinc and manganese were similar, regardless of the GA.

Table 2. Copper, Zinc, Iron, Calcium, Magnesium, Phosphorus and Manganese Concentration in Meconium as a Function of GA

Gestational age	Copper	Zinc	Iron	Calcium	Magnesium	Phosphorus	Manganese
24–28 weeks	113.2±19.4 (5)	156.4*±50.8 (5)	76.3±15.6 (5)	3962*$^{+}$±1037 (5)	2359±572 (5)	168.8±34.2 (5)	9.5±4.1 (5)
29–33 weeks	154.2***±11.4 (7)	282.1±60.8 (7)	68.9±11.2 (7)	1607±273 (8)	3005±399 (8)	145.0±25.1 (8)	15.5±2.6 (8)
34–37 weeks	115.5*±8.2 (12)	281.5±39.4 (12)	114.5**±19.2 (12)	2187±356 (12)	3299±413 (11)	164.4±30.8 (11)	31.4±8.9 (11)
38–42 weeks	90.3±9.3 (9)	365.4±55.6 (9)	47.6±7.7 (9)	1611±285 (8)	3314±363 (9)	114.7±25.1 (8)	35.8±8.3 (8)

Data expressed as μg/g dry meconium and as means±SEM.
(n)=number of specimens analyzed.
* p<0.05; ** p<0.01; *** p<0.001 vs. 38–42 weeks (Kruskal-Wallis). $^{+}$ p<0.05 vs. 29 to 33 weeks.

Table 3. Copper, Zinc, Iron, Calcium, Magnesium, Phosphorus and Manganese Concentration in Meconium as a Function of Birth Weight

Weight range	Copper	Zinc	Iron	Calcium	Magnesium	Phosphorus	Manganese
<1500 g	130.1**±14.4 (8)	191.1±44.1 (8)	78.6±10.6 (8)	2822±835 (8)	2777±479 (8)	162.1±25.7 (8)	11.3±2.9 (8)
1500–1999 g	139.7*±12.9 (8)	268.7±43.9 (8)	94.9±21.9 (8)	1663±244 (8)	3149±500 (8)	136.7±15.7 (8)	25.3±9.3 (8)
2000–2499 g	114.5±8.1 (8)	343.9±59.0 (9)	102.9±21.8 (9)	2329±289 (9)	3026±357 (8)	162.6±64.6 (8)	31.1±10.3 (8)
>2500 g	85.5±9.4 (9)	308.2±51.6 (9)	49.9±9.1 (9)	1869±487 (8)	3370±404 (9)	129.8±24.3 (8)	32.7±7.3 (8)

Data expressed as μg/g dry meconium and as means±SEM.
(n)=number of specimens analyzed.
** p<0.01 vs. >2500 g (Kruskal-Wallis).

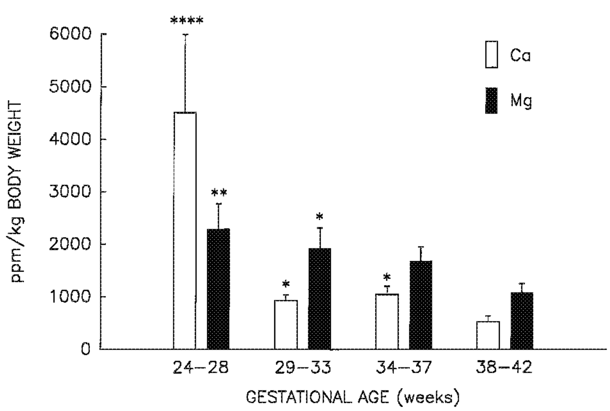

Fig. 1. Birth weight-adjusted concentration of calcium (Ca) and magnesium (Mg) in the meconium of infants of various GA. The dispersion brackets correspond to ±SEM. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 against the values of the 38 to 42 week group. The number of samples per group is the same as that of Table 2.

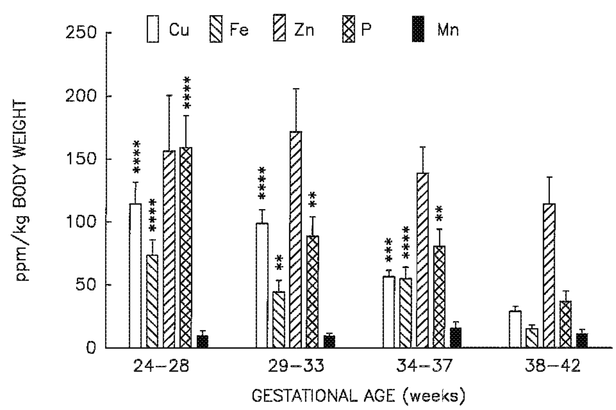

Fig. 2. Birth weight-adjusted concentration of copper (Cu), iron (Fe), zinc (Zn), phosphorus (P) and manganese (Mn) in the meconium of newborn infants. The remaining information is the same as that of Fig. 1.

DISCUSSION

The data presented here show that substantial changes occur in the mineral content of meconium, when considered either as a function of GA or of infant birth weight. In this study we have extended previously incomplete observations on the mineral composition of meconium [1–4] which did not precisely discriminate the GA or the birth weight of premature infants in their comparison with full term newborns.

Minerals account for no more than 4% of the wet weight of the meconium [8], or approximately 16% of its dry weight. The concentration of minerals in the meconium may reflect: a) the rates of placental transport of minerals and maternal sufficiency of the same; b) the equilibrium between the nutrient transferred to the fetus, its utilization and distribution in fetal tissues; c) its excretion capability; and d) pharmacologic use of inorganic salts, e.g., magnesium, or mineral supplementation during gestation, and especially during the antepartum period. It can be assumed that the elements appearing in the meconium are minerals no longer available to the fetus. In consequence, the composition of these first postnatal excreta can be considered to partially reflect the nutritional "history" of the fetus, since all inorganic elements are received from the mother. A premature infant, other than the understandable developmental immaturity signified by its untimely birth, has not accrued the full complement of the inorganic macro- and micronutrients with which the full term infant is endowed.

The transport of mineral elements across the placenta has been studied to a far lesser extent than other placental transport processes. The recent availability of stable (non-radioactive) isotopes has opened greater possibilities [9]. However, the inherent invasiveness of the approach has discouraged the extension of animal studies to humans. The growth milestones of the fetus in utero can be fairly accurately monitored by ultrasonography [10]. Nevertheless size, estimated weight and head circumference do not necessarily reflect possible intrauterine nutritional deficiencies. One of the potential causes for subclinical mineral insufficiency is the different type of transport mechanisms operating for macro- and microelements. Characteristically, certain minerals, such as zinc, are known to be transported across the placenta against a concentration gradient [11]. The observation of a higher zinc concentration in the meconium of the full term infants, as compared to that of extremely premature infants, is consistent with a greater rate of zinc transport late in gestation and a more effective uphill gradient for this element [12], which is maintained throughout the third trimester. In contrast, copper, which has a downhill mother-to-fetus gradient in humans [13,14] and mammals [15], exhibited smaller changes in absolute concentration as GA or birth weight increased, but a significant decrease in birth weight adjusted values. A similar pattern was observed for iron and phosphorus.

The concentration of magnesium in meconium was noted to remain constant, in both the GA groups and the birth weight categories. Although no discrimination was attempted between infants of mothers who received or did not receive magnesium sulfate antepartum, the remarkable uniformity of meconium magnesium concentration suggests that, in spite of possible systemic effects on the newborn, the amounts appearing in the fetal gastrointestinal tract are not affected.

Meconium has been used as a means to monitor cocaine, heroin and cannabinoids use by the mother, proving to be a more reliable indicator of prenatal exposure to xenobiotics than the urine of the newborn [16–19]. Regarding toxic metal exposure of the newborn, such as cadmium and lead, stool analysis in populations at risk for inorganic contaminants has been shown to be an effective way of estimating oral intake of these elements [20]. There appears to be no precedent for the systematic examination of fecal material of infants or children to determine intrauterine exposure to heavy metals, although lead and aluminum have been quantitated in meconium [4]. In contrast with the paucity of data on minerals, meconium has been studied to determine the ontogenesis of intestinal enzymes, particularly disaccharidases and proteolytic enzymes which are relevant to the understanding of the development of the gastrointestinal system [8,21,22].

The results of this study could potentially serve to: a) establish better defined normative data on meconium mineral concentration in the newborn of GA's spanning the last trimester; b) aid in the detection of gastrointestinal developmental abnormalities that might alter the mineral composition of the meconium; c) serve as the basis for the examination of the meconium of intrauterine growth retarded infants for possible abnormalities in the content of any of the essential elements. It is conceivable that analysis of meconium could be a yet unexplored non-invasive approach to further clarify unanswered questions on the placental transport of minerals. In addition, by investigating meconium in multiple births and the possible relationship between concentration of essential elements in meconium and cord blood, nutrient supply processes of the fetus during the latter part of gestation could be further clarified.

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